REGULAR RESEARCH ARTICLE

# Blood D-Amino Acid Oxidase Levels Increased With Cognitive Decline Among People With Mild Cognitive Impairment: A Two-Year Prospective Study

## Chieh-Hsin Lin, Hsien-Yuan Lane

Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan (Dr Lin); School of Medicine, Chang Gung University, Taoyuan, Taiwan (Dr Lin); Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan (Dr Lin); Department of Psychiatry & Brain Disease Research Center, China Medical University Hospital, Taichung, Taiwan (Dr Lane); Department of Psychology, College of Medical and Health Sciences, Asia University, Taichung, Taiwan (Dr Lane).

Correspondence: Hsien-Yuan Lane, MD, PhD, Department of Psychiatry, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 404, Taiwan (hylane@gmail.com).

## Abstract

**Background:** Dysregulation of N-methyl-D-aspartate receptor (NMDAR) neurotransmission has been reported to be implicated in the pathogenesis of Alzheimer's disease (AD). D-amino acid oxidase (DAO), responsible for degradation of NMDAR-related D-amino acids such as D-serine, regulates NMDAR function. A cross-section study found that serum DAO levels were positively related with the severity of cognitive aging among elderly individuals. This 2-year prospective study aimed to explore the role of DAO levels in predicting the outcome of patients with very early-phase AD, such as mild cognitive impairment (MCI).
**Methods:** Fifty-one patients with MCI and 21 healthy individuals were recruited. Serum DAO levels and cognitive function, measured by the AD assessment scale-cognitive subscale and the Mini-Mental Status Examination, were monitored every 6 months. We employed multiple regressions to examine the role of DAO concentration in cognitive decline in the 2-year period.
**Results:** From baseline to endpoint (24 months), serum DAO levels increased significantly, and cognitive ability declined according to both cognitive tests in the MCI patients. Among the healthy individuals, DAO concentrations also increased and Mini-Mental Status Examination scores declined; however, AD assessment scale-cognitive subscale scores did not significantly change. Further, DAO levels at both months 12 and 18 were predictive of cognitive impairment at month 24 among the MCI patients.
**Conclusions:** To our knowledge, this is the first study to demonstrate that blood DAO levels increased with cognitive deterioration among the MCI patients in a prospective manner. If replicated by future studies, blood DAO concentration may be regarded as a biomarker for monitoring cognitive change in the patients with MCI.

**Keywords:** Biomarker, D-amino acid oxidase (DAO), mild cognitive impairment (MCI), N-methyl-D-aspartate receptor (NMDAR)

**Significance Statement**

N-methyl-D-aspartate receptor (NMDAR) neurotransmission is implicated in Alzheimer's disease. D-amino acid oxidase (DAO) regulates NMDAR function. A previous cross-section study found that DAO levels were related with the severity of cognitive aging among elderly individuals. This is the first study, to our knowledge, to demonstrate that blood DAO levels increased with cognitive deterioration among the MCI patients in a prospective manner in the 2-year period. If replicated by future studies, blood DAO concentration may be regarded as a biomarker for monitoring cognitive change in patients with MCI.

## Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder, accounting for more than 60%–80% of all cases of dementia; noteworthy, the number of patients with AD worldwide has been increasing rapidly (Hinton et al., 2020; Engin and Engin, 2021). Furthermore, heterogeneous etiologies (including atypical amyloid β [Aβ] deposition, neurofibrillary tangles of tau proteins, inflammation, oxidative stress, and altered neurotransmission) may be implicated in AD (Lewczuk et al., 2020; Zarrouk et al., 2020; Cheng et al., 2021).

Glutamate, the principal excitatory neurotransmitter in mammalian brain (McDonald and Johnston, 1990), plays a critical role in regulating neurogenesis, neurite outgrowth and synaptogenesis, neuronal survival, and synaptic plasticity (Mattson, 2008; Gan and Sudhof, 2019; Chang et al., 2020). Optimal activation of the N-methyl-D-aspartate receptors (NMDARs), a subtype of ionotropic glutamate receptor, is required for synaptic plasticity, learning, and cognition (Kumar, 2015; Clifton et al., 2019). Overactivation of NMDAR results in neurotoxicity; on the other hand, insufficient NMDAR-mediated neurotransmission leads to loss of neuronal plasticity in the aging brain and cognitive decline in the elderly (Lin and Lane, 2019; Pinheiro and Faustino, 2019; Le Douce et al., 2020). In patients with AD, glutamate levels were found to be reduced in brain tissue and the cerebrospinal fluid (Lowe et al., 1990; Martinez et al., 1993). Whereas the levels of D-serine (an endogenous full agonist of the glycine site of NMDAR) were higher in the cerebrospinal fluid of the probable AD patients than in healthy controls (Madeira et al., 2015), D-serine levels were lower in the serum of the AD patients (Hashimoto et al., 2004). D-serine administration also improved spatial memory, learning, and problem solving in older adults (Avellar et al., 2016) and alleviated the cognitive impairment of Aβ1-42 injected mice (Liu et al., 2020). Moreover, the NMDAR density declined with age (Segovia et al., 2001), and Aβ downregulated the surface expression of NMDARs (Snyder et al., 2005; Kurup et al., 2010). These pieces of evidence lend support to the dysfunctional NMDAR hypothesis of AD (Snyder et al., 2005; Kurup et al., 2010; Cheng et al., 2021).

For detecting AD in its earliest clinical stage, the term of mild cognitive impairment (MCI), a slight cognitive impairment, was developed (Bowen et al., 1997). MCI, especially amnestic MCI, is a prodromal phase or risk factor of AD (Petersen, 2011; Boeve, 2012; Lane et al., 2021). Brain pathology changes are observed much earlier than the cognitive and functional deterioration in AD patients (Petersen, 2011; Lin et al., 2014; Chiang et al., 2021; Guzman-Martinez et al., 2021). Therefore, it is crucial to discover clinically feasible biomarkers to predict or monitor the outcome or course of MCI (Chiang et al., 2021; Liss et al., 2021).

D-amino acid oxidase (DAO), a flavoenzyme, is responsible in degrading D-amino acids, mainly D-serine and D-alanine (Fukui and Miyake, 1992; Sasabe et al., 2012). Inhibiting the activity of DAO is one of the approaches to activate NMDARs (Hashimoto et al., 2009; Howley et al., 2017; Hsu et al., 2018). Previous randomized, double-blind, placebo-controlled trials demonstrated that sodium benzoate, a DAO inhibitor, exceeded placebo in improving the cognitive function in patients with early-phase AD (MCI or mild AD) (Lin et al., 2014) and in a portion of patients with later-phase dementia (Lin et al., 2019, 2020, 2021). The growing body of evidence suggests that DAO may play an important role in the process of cognitive aging. A cross-section study showed that serum DAO levels were positively related to the severity of cognitive aging among elderly individuals (including healthy elderly, MCI, mild AD, and moderate to severe AD) (Lin et al., 2017). Whether DAO could serve as a potential biomarker in predicting or monitoring the outcome or course of MCI needs further longitudinal studies. This 2-year prospective study aimed to examine whether serum DAO levels changed with cognitive decline in people with MCI.

## METHODS

### Participants

Patients and healthy controls were screened and enrolled from Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, which is a major medical center in Taiwan. The study was approved by the institutional review board of the hospital and conducted in accordance with the current revision of the Declaration of Helsinki. All participants (both patients and healthy individuals) were evaluated by research psychiatrists after a thorough medical workup.

Participants were enrolled in this study if they (1) were ethnic Han Chinese, aged 50–100 years, (2) agreed to participate in the study and provided informed consent, (3) were physically healthy and had normal laboratory assessments (including routine blood and biochemical tests), and (4) had sufficient education to communicate effectively and ability to complete the assessments of the study.

We excluded participants if they had the following: (1) a history of significant cerebrovascular disease; (2) Hachinski Ischemic Score >4; (3) major neurological, psychiatric, or medical conditions other than MCI; (4) delusion, hallucination, or delirium symptoms; (5) substance (including alcohol) abuse or dependence; (6) severe visual or hearing loss; and (7) inability to follow the study protocol.

Patients with MCI fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for amnestic MCI (Lu et al., 2009) of a presumably degenerative nature defined as subjective memory complaint corroborated by an informant and insufficient global cognitive and functional impairment (McKhann et al., 1984), and had a Clinical Dementia Rating (Morris, 1993) score of 0.5. Healthy individuals had a Clinical Dementia Rating score of 0.

## Cognitive Function Assessments

We applied the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) (Rosen et al., 1984) and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) to evaluate cognitive function at months 0, 6, 12, 18, and 24.

The MMSE is a commonly used cognitive test for screening and measuring cognitive impairment in older people (Creavin et al., 2016). Its scores range from 0 (worst) to 30 (best).

The ADAS-cog is the most popular cognitive assessment instrument used in AD clinical trials (Cano et al., 2010). It consists of 11 tasks, including word recall, naming, commands, constructional praxis, ideational praxis, orientation, word recognition, remembering instructions, spoken language ability, word-finding difficulty, and comprehension. Its scores range from 0 (best) to 70 (worst). Compared with the MMSE, the ADAS-Cog is more sensitive and reliable and less influenced by educational level (Kueper et al., 2018).

## DAO Measurement

For both patients and healthy controls, blood sampling was conducted during 8 AM-12 PM after fasting for more than 8 hours. Ten mL of blood was collected by personnel trained in phlebotomy using a sterile technique. The blood specimens were processed immediately by centrifugation at $1000 \times g$. After centrifugation, serum was quickly dissected, immediately stored at –80°C until further measurement.

DAO protein concentrations in the serum were measured using a commercially available enzyme-linked immunosorbent assay kit (catalog no. SEJ298Hu) according to the manufacturer's recommended protocol (Cloud-Clone Corp, Houston, TX, USA). The detailed method has been described elsewhere (Lin et al., 2017). All DAO analyses were repeated twice.

## Statistical Analysis

All participants' clinical characteristics and DAO levels were presented as mean (SD) or number (percentage). We compared mean values between 2 groups by using the Mann-Whitney U test and percentages using the $\chi^2$ test.

The DAO levels and cognitive function assessments (MMSE and ADAS-cog scores) at baseline and at endpoint (at 2 years later) were compared by paired *t* test. Multiple linear regressions were used to discover independent factors associated with cognitive change in MCI patients (stepwise). All analyses

were performed using IBM SPSS, version 20 (IBM Corp., Armonk, NY, USA), and a 2-tailed $P<.05$ was considered statistically significant.

## RESULTS

Overall, 72 participants were enrolled, and they included 21 healthy individuals and 51 patients with MCI. The demographic, clinical, and laboratory data of both groups at baseline are summarized in Table 1.

Gender and age distributions were similar in the 2 groups. Female gender was the predominant gender of both groups. Compared with healthy individuals, MCI patients had shorter education durations (9.7 [mean] ± 2.5 [SD] vs 6.6 ± 4.3, $P<.001$), lower MMSE scores (29.0 ± 1.1 vs 25.1 ± 3.8, $P<.001$), higher ADAS-cog scores (3.3 ± 1.7 vs 9.5 ± 7.0, $P<.001$), and numerically (but statistically insignificant) higher serum DAO levels (50.6 ± 17.2 vs 61.8 ± 35.9 ng/mL, $P=.26$).

### DAO Levels and Cognitive Function Differed Significantly Between Baseline and Endpoint Among MCI Patients

Table 2 displays the changes of DAO concentration and cognitive function during the 2-year follow-up period.

In the MCI patients, serum DAO levels increased significantly (61.8 ± 35.9 to 117.7 ± 57.9 ng/mL, $P<.001$), and cognitive functions declined as measured by both tests (ADAS-cog [9.5 ± 7.0 to 11.5 ± 9.3, $P=.015$] and MMSE [25.1 ± 3.8 to 23.8 ± 4.2, $P=.004$] scores) from baseline to endpoint (month 24).

Among the healthy individuals, DAO concentrations also increased (50.6 ± 17.2 to 93.2 ± 42.4 ng/mL, $P<.001$) and MMSE scores declined (29.0 ± 1.1 to 28.2 ± 1.3, $P=.029$) from baseline to endpoint; however, ADAS-cog scores did not change significantly (3.3 ± 1.7 to 3.1 ± 1.5, $P=.60$).

### DAO Levels Significantly Influenced Cognitive Decline During 2 Years Among the MCI Patients

We tested whether DAO levels were able to affect cognitive decline during the 2-year period among the MCI patients.

Table 3 presents multiple linear regression analyses of independent factors (including age, gender, education duration, and DAO concentration at each visit) associated with cognitive change from baseline to endpoint in MCI patients (stepwise). The results showed that DAO levels at both months 12 and 18

**Table 1.** Demographic Characteristics of the Overall Cohort (n = 72) at Baseline

|  | Healthy elderly (n = 21) | MCI patients (n = 51) | P |
|---|---|---|---|
| Demographics |  |  |  |
|   CDR, mean (SD) | 0 | 0.5 |  |
|   Gender, female, n (%) | 15 (71.4) | 35 (68.6) | 1.000[a] |
|   Age, y, mean (SD) | 67.9 (8.1) | 70.5 (8.4) | .226[b] |
|   Education, y, mean (SD) | 9.7 (2.5) | 6.6 (4.3) | <.001[c] |
|   MMSE, mean (SD) | 29.0 (1.1) | 25.1 (3.8) | <.001[c] |
|   ADAS-cog, mean (SD) | 3.3 (1.7) | 9.5 (7.0) | <.001[c] |
| DAO level, ng/mL, mean (SD) | 50.6 (17.2) | 61.8 (35.9) | .257[c] |

Abbreviations: ADAS-cog, the Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR, Clinical Dementia Rating; DAO, D-amino acid oxidase; MCI, mild cognitive impairment; MMSE, Mini Mental Status Examination.

[a]Fisher's Exact test.
[b]t test.
[c]Mann-Whitney U test.

**Table 2.** Changes of DAO Levels and Cognitive Function During the 2-year Period

| Variable | DAO level, ng/mL | ADAS-cog | MMSE |
|---|---|---|---|
| Healthy elderly (n = 21) | | | |
| Baseline | 50.6 (17.2) | 3.3 (1.7) | 29.0 (1.1) |
| 6 mo | 76.5 (35.5) | 2.9 (1.3) | 28.6 (1.5) |
| 12 mo | 94.2 (64.7) | 3.1 (1.9) | 28.2 (1.0) |
| 18 mo | 103.3 (56.3) | 2.9 (1.4) | 28.4 (1.2) |
| 24 mo | 93.2 (42.4) | 3.1 (1.5) | 28.2 (1.3) |
| P value of paired t test (baseline vs 24 mo) | <.001 | .596 | .029 |
| MCI patients (n = 51) | | | |
| Baseline | 61.8 (35.9) | 9.5 (7.0) | 25.1 (3.8) |
| 6 mo | 78.1 (60.5) | 8.9 (5.9) | 25.4 (3.3) |
| 12 mo | 91.0 (39.9) | 9.5 (6.3) | 24.8 (3.9) |
| 18 mo | 95.3 (48.8) | 10.7 (8.2) | 24.1 (4.3) |
| 24 mo | 117.7 (57.9) | 11.5 (9.3) | 23.8 (4.2) |
| P value of paired t test (baseline vs 24 mo) | <.001 | .015 | .0004 |

Abbreviations: ADAS-cog, the Alzheimer's Disease Assessment Scale-Cognitive Subscale; DAO, D-amino acid oxidase; MCI, mild cognitive impairment; MMSE, Mini Mental Status Examination.
The values in parentheses are SD values.

**Table 3.** Multiple Linear Regression Analyses of Independent Factors (Including Baseline DAO level) Associated with Cognitive Change, Measured by ADAS-Cog Score Change From Baseline to Endpoint at Month 24, in MCI Patients (Stepwise)

| MCI patients (N = 51) | | | |
|---|---|---|---|
| Variable | B (SE) | t | P |
| DAO level at 12 mo, ng/mL | 0.043 (0.016) | 2.739 | .009 |
| DAO level at 18 mo, ng/mL | 0.031 (0.013) | 2.323 | .025 |
| Adjusted R square = 0.259 | | | |

Abbreviations: ADAS-cog, the Alzheimer's Disease Assessment Scale-Cognitive Subscale; B, Beta (the slope of the regression line); DAO, D-amino acid oxidase; MCI, mild cognitive impairment.
The regression model was adjusted by age, gender, education, and DAO level at each visit. Significant variables are shown as P < .05.

were positively associated with ADAS-Cog score change from baseline to endpoint (month 24). Other factors (age, gender, and education duration) did not significantly influence cognitive change. That is, higher DAO levels at month 12 and month 18 were predictive of cognitive decline at month 24 among the MCI patients.

## Discussion

To the best of our knowledge, this is the first study to prospectively follow blood DAO levels during the AD-related illness course. In accordance with the findings from the previous cross-section study, which found that serum DAO levels were positively related to the severity of cognitive aging among elderly individuals (Lin et al., 2017), the current study demonstrated that serum DAO levels increased from baseline (month 0) to endpoint (month 24) among the MCI patients and among the healthy elderly individuals (Table 2). Of note, DAO levels kept rising from month 12 (mean: 91.0 ng/mL) to month 24 (117.7 ng/mL) among the MCI patients, but kept constant from month 12 (mean: 94.2 ng/mL) to month 24 (93.2 ng/mL) among the healthy elderly (Table 2).

The results of the present study also showed that DAO levels at both months 12 and 18 (but not at an earlier time slot) were positively associated with ADAS-Cog score change from baseline

to month 24. Other factors (age, gender, and education duration) did not significantly affect cognitive change (Table 3). If confirmed by further studies, higher DAO levels at month 12 may be able to serve as a predictor for cognitive decline at month 24 among the MCI patients.

In addition, the present study indicated that cognitive performance in both cognitive tests (ADAS-cog and MMSE) deteriorated among the MCI patients in the 2-year follow-up period. On the other hand, among the healthy elderly individuals, MMSE scores declined from baseline to endpoint; however, ADAS-cog scores did not significantly change (Table 2). Of note, ADAS-cog scores significantly increased in MCI patients after 2-year follow-up but did not change significantly among the healthy elderly (Table 2), suggesting that ADAS-cog may be able to differentiate the MCI course from normal aging.

The ADAS-cog is the most popular cognitive assessment instrument used in AD clinical trials (Cano et al., 2010). Its responsiveness for MCI studies deserves more studies (Skinner et al., 2012; Montero-Odasso et al., 2018; Nishimaki et al., 2018; Lane et al., 2021). The current study lends support to the notion that ADAS-cog can be also applied in MCI trials, particularly those with longer treatment or follow-up duration such as 2 years.

These findings also suggest the importance of periodically monitoring DAO concentration as well as cognitive function for the MCI patients in not only clinical service but also clinical trials. Moreover, the findings could be a basis for setting up precision medicine in the field of cognitive aging in the future.

### Strength and Limitations

The main strength of the current study is that we examined longitudinal effects of DAO levels in cognitive function in the MCI patients. Second, we applied not only the MMSE (Folstein et al., 1975) but also the ADAS-cog (which can provide more comprehensive cognitive evaluation) (Rosen et al., 1984) in this follow-up study.

There are also limitations of the present study. First, the peripheral blood-CNS relationship of DAO requires further studies in patients with MCI. Second, the participants in the present study were an ethnic Han Chinese cohort. Our study findings may not be generalizable to other populations. Third, the number of participants was small. Finally, the follow-up duration (24 months)

was modest. Because serum DAO concentration may gradually increase during the MCI phase, whether it also escalates during the AD phase deserves more studies.

### Clinical Implication and Future Direction

MCI stands for the transitional state between normal aging and dementia (Petersen, 2011). It is vital to find a clinically applicable blood biomarker for predicting and monitoring the illness course. The present study suggests that blood DAO concentration may be a feasible marker in assisting physicians in monitoring early cognitive aging and predicting of its outcome.

Further studies with large sample sizes and longer follow-up duration are needed for more thoroughly elucidating the role of DAO in cognitive aging.

## Conclusions

This study demonstrated that blood DAO levels increased with cognitive deterioration among the MCI patients in a prospective manner; moreover, DAO levels at month 12 were predictive of cognitive decline at month 24. Nonetheless, further studies with a larger sample size and longer follow-up duration are required to evaluate the temporal relationship between DAO levels and the cognitive-aging progress. If reconfirmed by future studies, blood DAO concentration may be able to serve as a biomarker for monitoring cognitive change in MCI.

## Acknowledgments

## Interest Statement

The authors declare that there is no conflict of interest.

## References

Avellar M, Scoriels L, Madeira C, Vargas-Lopes C, Marques P, Dantas C, Manhaes AC, Leite H, Panizzutti R (2016) The effect of D-serine administration on cognition and mood in older adults. Oncotarget 7:11881–11888.

Boeve BF (2012) Mild cognitive impairment associated with underlying Alzheimer's disease versus Lewy body disease. Parkinsonism Relat Disord 18:S41–S44.

Bowen J, Teri L, Kukull W, McCormick W, McCurry SM, Larson EB (1997) Progression to dementia in patients with isolated memory loss. Lancet 349:763–765.

Cano SJ, Posner HB, Moline ML, Hurt SW, Swartz J, Hsu T, Hobart JC (2010) The ADAS-cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum and its parts. J Neurol Neurosurg Psychiatry 81:1363–1368.

Chang CH, Lin CH, Lane HY (2020) D-glutamate and gut microbiota in Alzheimer's disease. Int J Mol Sci 21:2676.

Cheng YJ, Lin CH, Lane HY (2021) Involvement of cholinergic, adrenergic, and glutamatergic network modulation with cognitive dysfunction in Alzheimer's disease. Int J Mol Sci 22:2283.

Chiang TI, Yu YH, Lin CH, Lane HY (2021) Novel biomarkers of Alzheimer's disease: based upon N-methyl-D-aspartate receptor hypoactivation and oxidative stress. Clin Psychopharmacol Neurosci 19:423–433.

Clifton NE, Trent S, Thomas KL, Hall J (2019) Regulation and function of activity-dependent homer in synaptic plasticity. Mol Neuropsychiatry 5:147–161.

Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, Thom VM, Nash KJ, Elhamoui H, Milligan R, Patel AS, Tsivos DV, Wing T, Phillips E, Kellman SM, Shackleton HL, Singleton GF, Neale BE, Watton ME, Cullum S (2016) Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database Syst Rev 1:CD011145.

Engin AB, Engin A (2021) Alzheimer's disease and protein kinases. Adv Exp Med Biol 1275:285–321.

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.

Fukui K, Miyake Y (1992) Molecular cloning and chromosomal localization of a human gene encoding D-amino-acid oxidase. J Biol Chem 267:18631–18638.

Gan KJ, Sudhof TC (2019) Specific factors in blood from young but not old mice directly promote synapse formation and NMDA-receptor recruitment. Proc Natl Acad Sci U S A 116:12524–12533.

Guzman-Martinez L, Calfio C, Farias GA, Vilches C, Prieto R, Maccioni RB (2021) New frontiers in the prevention, diagnosis, and treatment of Alzheimer's disease. J Alzheimers Dis 82:S51–S63.

Hashimoto K, Fukushima T, Shimizu E, Okada S, Komatsu N, Okamura N, Koike K, Koizumi H, Kumakiri C, Imai K, Iyo M (2004) Possible role of D-serine in the pathophysiology of Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 28:385–388.

Hashimoto K, Fujita Y, Horio M, Kunitachi S, Iyo M, Ferraris D, Tsukamoto T (2009) Co-administration of a D-amino acid oxidase inhibitor potentiates the efficacy of D-serine in attenuating prepulse inhibition deficits after administration of dizocilpine. Biol Psychiatry 65:1103–1106.

Hinton L, Nguyen H, Nguyen HT, Harvey DJ, Nichols L, Martindale-Adams J, Nguyen BT, Nguyen BTT, Nguyen AN, Nguyen CH, Nguyen TTH, Nguyen TL, Nguyen ATP, Nguyen NB, Tiet QQ, Nguyen TA, Nguyen PQ, Nguyen TA, Pham T (2020) Advancing family dementia caregiver interventions in low- and middle-income countries: a pilot cluster randomized controlled trial of Resources for Advancing Alzheimer's Caregiver Health in Vietnam (REACH VN). Alzheimers Dement 6:e12063.

Howley E et al. (2017) Assessment of the target engagement and D-serine biomarker profiles of the D-amino acid oxidase inhibitors sodium Benzoate and PGM030756. Neurochem Res 42:3279–3288.

Hsu WY, Lane HY, Lin CH (2018) Medications used for cognitive enhancement in patients with schizophrenia, bipolar disorder, Alzheimer's disease, and Parkinson's disease. Front Psychiatry 9:91.

Kueper JK, Speechley M, Montero-Odasso M (2018) The Alzheimer's Disease Assessment Scale-Cognitive Subscale

(ADAS-Cog): modifications and responsiveness in pre-dementia populations. A narrative review. J Alzheimers Dis 63:423–444.

Kumar A (2015) NMDA receptor function during senescence: implication on cognitive performance. Front Neurosci 9:473.

Kurup P, Zhang Y, Venkitaramani DV, Xu J, Lombroso PJ (2010) The role of STEP in Alzheimer's disease. Channels 4:347–350.

Lane HY, Tu CH, Lin WC, Lin CH (2021) Brain activity of benzoate, a D-amino acid oxidase inhibitor, in patients with mild cognitive impairment in a randomized, double-blind, placebo controlled clinical trial. Int J Neuropsychopharmacol 24:392–399.

Le Douce J, Maugard M, Veran J et al. (2020) Impairment of glycolysis-derived L-serine production in astrocytes contributes to cognitive deficits in Alzheimer's disease. Cell Metab 31:503–517.e508.

Lewczuk P, Lukaszewicz-Zajac M, Mroczko P, Kornhuber J (2020) Clinical significance of fluid biomarkers in Alzheimer's disease. Pharmacol Rep 72:528–542.

Lin CH, Chen PK, Chang YC, Chuo LJ, Chen YS, Tsai GE, Lane HY (2014) Benzoate, a D-amino acid oxidase inhibitor, for the treatment of early-phase Alzheimer disease: a randomized, double-blind, placebo-controlled trial. Biol Psychiatry 75:678–685.

Lin CH, Chen PK, Wang SH, Lane HY (2019) Sodium benzoate for the treatment of behavioral and psychological symptoms of dementia (BPSD): a randomized, double-blind, placebo-controlled, 6-week trial. J Psychopharmacol 33:1030–1033.

Lin CH, Chen PK, Wang SH, Lane HY (2021) Effect of sodium benzoate on cognitive function among patients with behavioral and psychological symptoms of dementia: secondary analysis of a randomized clinical trial. JAMA Netw Open 4:e216156.

Lin CH, Lane HY (2019) The role of N-methyl-D-aspartate receptor neurotransmission and precision medicine in behavioral and psychological symptoms of dementia. Front Pharmacol 10:540.

Lin CH, Yang HT, Chen PK, Wang SH, Lane HY (2020) Precision medicine of sodium benzoate for the treatment of behavioral and psychological symptoms of dementia (BPSD). Neuropsychiatr Dis Treat 16:509–518.

Lin CH, Yang HT, Chiu CC, Lane HY (2017) Blood levels of D-amino acid oxidase vs. D-amino acids in reflecting cognitive aging. Sci Rep 7:14849.

Liss JL et al. (2021) Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis. J Intern Med 290:310–334.

Liu H, Li S, Yang C, Jia H, Gu Z, Tu X, Tian S, Liu J, Li G, Ma Y (2020) D-serine ameliorates motor and cognitive impairments in beta-amyloid 1-42 injected mice by inhibiting JNK signaling pathway. J Chem Neuroanat 109:101852.

Lowe SL, Bowen DM, Francis PT, Neary D (1990) Ante mortem cerebral amino acid concentrations indicate selective degeneration of glutamate-enriched neurons in Alzheimer's disease. Neuroscience 38:571–577.

Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL, Alzheimer's Disease Cooperative Study G (2009) Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology 72:2115–2121.

Madeira C, Lourenco MV, Vargas-Lopes C, Suemoto CK, Brandao CO, Reis T, Leite RE, Laks J, Jacob-Filho W, Pasqualucci CA, Grinberg LT, Ferreira ST, Panizzutti R (2015) d-serine levels in Alzheimer's disease: implications for novel biomarker development. Transl Psychiatry 5:e561.

Martinez M, Frank A, Diez-Tejedor E, Hernanz A (1993) Amino acid concentrations in cerebrospinal fluid and serum in Alzheimer's disease and vascular dementia. J Neural Transm Park Dis Dement Sect 6:1–9.

Mattson MP (2008) Glutamate and neurotrophic factors in neuronal plasticity and disease. Ann N Y Acad Sci 1144:97–112.

McDonald JW, Johnston MV (1990) Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. Brain Res Brain Res Rev 15:41–70.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944.

Montero-Odasso M et al. (2018) SYNERGIC TRIAL (SYNchronizing Exercises, Remedies in Gait and Cognition) a multi-centre randomized controlled double blind trial to improve gait and cognition in mild cognitive impairment. BMC Geriatr 18:93.

Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43:2412–2414.

Nishimaki K, Asada T, Ohsawa I, Nakajima E, Ikejima C, Yokota T, Kamimura N, Ohta S (2018) Effects of molecular hydrogen assessed by an animal model and a randomized clinical study on mild cognitive impairment. Curr Alzheimer Res 15:482–492.

Petersen RC (2011) Clinical practice. Mild cognitive impairment. N Engl J Med 364:2227–2234.

Pinheiro L, Faustino C (2019) Therapeutic strategies targeting amyloid-beta in Alzheimer's disease. Curr Alzheimer Res 16:418–452.

Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. Am J Psychiatry 141:1356–1364.

Sasabe J, Miyoshi Y, Suzuki M, Mita M, Konno R, Matsuoka M, Hamase K, Aiso S (2012) D-amino acid oxidase controls motoneuron degeneration through D-serine. Proc Natl Acad Sci U S A 109:627–632.

Segovia G, Porras A, Del Arco A, Mora F (2001) Glutamatergic neurotransmission in aging: a critical perspective. Mech Ageing Dev 122:1–29.

Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, Gibbons LE, Alzheimer's Disease Neuroimaging I (2012) The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. Brain Imaging Behav 6:489–501.

Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P (2005) Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci 8:1051–1058.

Zarrouk A, Hammouda S, Ghzaiel I, Hammami S, Khamlaoui W, Ahmed SH, Lizard G, Hammami M (2020) Association between oxidative stress and altered cholesterol metabolism in Alzheimer's disease patients. Curr Alzheimer Res 17:823–834.